REMARKS

Applicants thank the Examiner for his making time for a phone interview to discuss the proposed claim amendments and explanation how the amendments and an exemplary reference address the points in the remaining 112 1st ¶ rejection. The subject phone interview is scheduled for Wednesday, October 17 at 1PM (EST).

The proposed amendment incorporates the substance of Claim 76 into Claim 70, resulting in the cancellation of Claim 76 and amendments to correct the dependencies of Claims 77, 78 and 81, which had formerly depended on the now cancelled Claim 76. The proposed amendment to Claim 70, that incorporates the substance of the now propcsed to be cancelled Claim 76, indicates that the cell membrane-impermeant, potent specific inhibitor of MN/CA IX used in the diagnostic/prognostic method of Claim 70 is "conjugated to a label or a visualizing means," and that "said label or said visualizing means on cells in [a vertebrate] . . . sample" is detected or detected and quantified. As a result of that proposed amendment, all the pending claims 67-70, 72-75 and 77-90 would concern methods comprising the use of a MN/CA IX-specific inhibitor which is either "conjugated to a label or a visualizing means" [Claims

67, 68, 70, 72-75, 77-82 and 86-88] or "linked to an imaging agent" [Claims 69, 83-85 and 89-90].

Based on the teachings in the instant specification, one of skill in the art would expect that a "label," "visualizing means" or "imaging agent" that is either conjugated or linked to a MN/CA IX-specific inhibitor would render said inhibitor to be even more selective for MN/CA IX rather than for other CA isoenzymes. The Specification teaches that MN/CA IX's active site is larger than any of the other widely distributed relevant carbonic anhydrase isoenzymes, such as CA I, CA II and CA IV. [See, for example, the Specification at least at page 9, lines 1-4; at page 50, lines 3-5; and at page 54, lines 6-8]. As the "label," "visualizing means," or "imaging agent" conjugated/linked to a MN/CA IX-specific inhibitor would render the inhibitor bulkier, one of skill in the art would expect that that bulkier compound would fit into the larger sized active site of MN/CA IX before it would fit into the smaller sized active sites of other CA IX isoenzymes, where it would have difficulty in fitting or be barred from fitting.

Such label-related increased selectivity of MN CA IX-specific inhibitors is shown by a comparison of the results of screening assays for Compound 5 (homosulfanilamide) of the instant invention when it is unconjugated and then when it is

conjugated to a label. Compound 5 is shown in Table 1 of the Specification (page 60, line 15) to have greater specificity towards MN/CA IX then to CA I, CA II and CA IV, but with a K_I of 103 nM (the preliminary screening result reported in Table 1), the unconjugated Compound 5 would not be considered to be a potent inhibitor of MN/CA IX in accordance with the pending claims, wherein such potency is established as "to be less than about 50 nanomolar. . . ." However, the accompanying reference, Svastova et al., FEBS Lett., 577: 439-445 (2004), shows that Compound 5 (homosulfanilamide) when conjugated to FITC [CAI #3 in Svastova et al.] has a K_I value against CA IX of 24 nM [Svastova et al., at page 440, top of col. 2], that is, the labeled Compound 5 is a potent inhibitor of MN/CA IX.

FITC-homosulfanilamide, an exemplary MN/CA IX-specific inhibitor conjugated to a label, is used to visualize CA IX on the surface of MDCK cells under conditions of hypoxia and not normoxia after 48 hours incubation [Svastova et al. 2004; Figure 2(C), at page 441]. MN/CA9 is known to be one of the most (if not the most) tightly regulated by hypoxia of all genes tested for such regulation. The selectivity of FITC-homosulfanilamide (an exemplary MN/CA IX-specific inhibitor conjugated to a label) for hypoxically-induced CA IX is additional evidence that supports that the claimed methods are adequately enabled.

Page 27, lines 1-6 of the Specification refers to experiments wherein FITC-labeled sulfonamides are "shown to bind to the surface of MN/CA IX transfected cells, and not to control cells, only in hypoxia but not in normoxia. Those experiments confirm that CA IX-specific inhibitors, such as the sulfonamide compounds described herein, can specifically target MN/CA IX under conditions characteristic of intratumoral microenvironments." [Emphasis added.] In that quote, "[t]hose experiments" are referring to the experiments of Svastova et al. 2004 (that is, the accompanying article). Applicants respectfully point out that the experiments of Svastova et al. support the imaging use of the CA IX inhibitors conjugated to labels such as FITC, as well as the improved specificity for CA IX of a labeled MN/CA IX-specific inhibitor over the unlabeled MN/CA IX-specific inhibitor. Such exemplary in vitro experiments also support the instant claims directed to in vivo imaging [Claims 69, 83-85 and 89-90].

In view of that Svastova et al. example, and disclosure in the Specification that the active site of CA IX is larger than that of other CAs tested, one of skill in the art would expect that a MN/CA IX-specific inhibitor conjugated to a "label," "visualizing means" or "imaging" agent would be more selective for CA IX than the unconjugated inhibitor.